H6

82. (New claim) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

REMARKS

Claims 25-27, 40, 44-50, 53-64 and 66-81 are stated by the Examiner to be pending in the present application. As a preliminary matter, however, in the response filed August 14, 2001, Applicants cancelled claims 40, 56, and 78, amended claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80, and added new claim 82. None of these amendments appear to have been entered. Accordingly, Applicants have, again, amended the claims in an identical manner. Upon entry of the present Amendment, claims 25-27, 44-50, 53-55, 57-64, 66-77, and 79-82 will be pending

Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. The present application, however contains no drawings. Accordingly, the "Attachment for PTO-948" is not relevant in the present application.

The Office Action points out the typographical error in reciting "proylene" in claims 54 and 76. Applicants have previously corrected the typographical error in claims 54 and 76 in the response filed August 14, 2001. To the extent that such amendment has not, in fact, been entered as requested, Applicants again make the amendments herein.

I. The Claimed Inventions Are Not Obvious

Claims 44-50 and 53-64 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of WO 97/05903 (hereinafter, the "Watts reference") in view of U.S. Patent No. 5,994,062 (hereinafter, the "Mulshine reference") and U.S. Patent No. 5,707,648 (hereinafter, the "Yiv reference"). The Office Action asserts that it would have been obvious to combine the composition of the Watts reference with the method of delivery of the Mulshine reference. The Office Action also asserts that it would have been further obvious modify the composition of the Watts reference by the addition of a fatty acid from the Yiv reference. Applicants

traverse the rejection and request reconsideration thereof because the reasons identified in the Office Action for motivation to combine the cited references are merely conclusory statements of the Examiner.

As a preliminary matter, Applicants take this opportunity to, again, correct the Examiner's continued misinterpretation of the Watts reference. The Office Action asserts at page 9 that the Watts reference teaches a "composition comprising a nucleic acid and a mixture of fatty acids." As pointed out during the interview with the Examiner and in the previously filed response, ***this is not true***! Rather, the Watts reference reports a drug in combination with a mixture "of a fatty acid having 6 to 16 carbon atoms or related mono/diglycerides and a pharmaceutically acceptable dispersing agent" (emphasis added) (see, page 5 of the Watts reference). Subsequent discussions with the Examiner resulted in an agreement that mono/diglycerides of fatty acids were not the same as the fatty acids themselves. Thus, the Watts reference does not teach or suggest the combination of a nucleic acid and at least two fatty acids as recited in claim 44 or the combination of a nucleic acid and capric acid or lauric acid having the modifications recited in claim 61. Noticeably absent from the Office Action is any citation that supports any of the assertions in the Office Action.

The only motivation for combining the Watts, Mulshine and Yiv references is the following text found at pages 10-11 of the Office Action:

> The combination of fatty acids taught by each of WO 97/05903 [the Watts reference] and US 5,707,648 [the Yiv reference] make obvious the combination of two or more fatty acids in a composition as taught in the instant claimed composition and methods, since it is obvious to combine the teachings of two compositions and methods to make a third composition which is merely the combination of the two compositions, namely, two or more fatty acids in the instant composition.

This conclusory statement amounts asserts that it is obvious to combine two compositions into a third composition because the third composition is the combination of the two compositions. This circular reasoning is wholly insufficient to establish the level of motivation to make out a *prima facie* case of obviousness. A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re*

Kotzab, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). "In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998). In no way can the circular reasoning provided in the Office Action suffice to establish the requisite level of motivation to combine the cited references to produce Applicants' claimed compositions.

In view of the lack of any credible reasons for motivation to combine the cited references, it is quite clear that the only motivation for combining the references in the manner suggested in the Office Action comes from Applicants' specification. Applicants note that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Under this standard, none of the prior art of record, alone or in any proper combination, discloses or suggests the present invention as defined by the amended claims. This is not to say that it is impossible to combine selected elements of several references to show the obviousness of an invention, however, there still must be a "suggestion or motivation in the prior art to make the selection." *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991) (claim held obvious in view of combined teachings of references showing elements for same purpose as claimed invention).

To the extent that the Examiner continues to carry forward the present obviousness rejection, Applicants again point out that the present specification provides unexpected and surprising results. In Example 3 of the specification, Formulation 1 (lauric acid; C12) and

Formulation 2 (capric acid; C10) each, alone, resulted in 5% absorption. When lauric acid and capric acid were combined in Formulation 3, however, absorption increased unexpectedly to 15%, which clearly indicates a synergistic effect. It is well-settled that evidence of unobvious or unexpected advantageous properties can be presented to rebut a *prima facie* case of obviousness. *In re Chupp*, 816 F.2d 643, 645, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987). Further, Applicants provide herewith a Declaration under 37 C.F.R. § 1.132 of Dr. Teng, a co-inventor of the present application. In his Declaration, Dr. Teng states that an experiment was performed along the lines of the experiment described in Example 4 of the present application. Rat jejunum, however, was used instead of rat ileum. Rats that were administered a composition comprising caprylic acid (C8) yielded 0.9% absorption and rats administered a composition comprising lauric acid (C12) yielded 8.3% absorption. Rats administered a composition comprising both caprylic acid and lauric acid, however, yielded 11% absorption. Dr. Teng asserts that such a combination produced a result greater than would have been expected in view of the individual absorptions obtained. Thus, Applicants have provided ample unexpected and surprising results.

Thus, the claimed compositions comprising at least two fatty acids are not obvious in view of the combination of cited references. First, the Office Action fails to provide sufficient motivation for combining the teachings of the Watts, Mulshine and Yiv references. Second, Applicants provide unexpected and surprising results. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. The Claims Are Clear And Definite

Claims 25-27, 56, 64, 78 and 80 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being vague and indefinite. Applicants traverse the rejection and respectfully request reconsideration in view of the amended claims.

As a preliminary matter, each of these rejections has, in fact, been addressed in Applicants' response dated August 14, 2001. They are repeated here for the sake of completeness.

The Office Action asserts that claim 25 is missing an essential step in that the claim allegedly fails to recite a step for administering the composition to the alimentary canal. As pointed

out during the interview and in the previously filed response, however, claim 25 recites "A method ...comprising **administering**..." (emphasis added). Thus, the step of "administering" is, indeed, recited in claim 25. Thus, claim 25 is definite within the meaning of § 112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

The Office Action asserts that the breadth of the ranges of the modifications recited in claims 61 and 64 are considered indefinite. Applicants have amended claims 61 and 64 in the previously filed response, as recommended during the interview. Thus, the range of modifications recited in claim 64 falls within the scope of the range of modifications recited in claim 61. To the extent that the amendments to claims 61 and 64 have not been entered, they are made herein again.

Claim 66 has been amended in the previously filed response as suggested during the interview to replace the term "oligonucleotide" with the phrase "nucleic acid" to more properly provide antecedent basis. To the extent that the amendment to claim 66 has not been entered, it is made herein again.

The Office Action asserts that claims 56 and 78 lack antecedent basis for the phrase "when administered to an animal." Claims 56 and 78 have, in fact, been cancelled.

In addition, claim 80 has been amended again, as suggested in the Office Action, to insert the term "further." No change in claim scope has been effected.

In view of the comments and amendments to the claims, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The Claimed Inventions Are Enabled

Claims 25-27, 40 and 66-81 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable the full scope of the claimed invention. Applicants traverse the rejection and request reconsideration thereof because one skilled in the art would be able to practice the claimed inventions without being required to perform undue experimentation.

The Office Action asserts at page 6:

> Enablement for the full scope of the specification is required for enablement of the claims as written, and claims which recite the use of a nucleic acid must be enabled for all of the stated uses of the nucleic acid.

The Office Action concludes that because Applicants' specification mentions gene therapy, and gene therapy is allegedly not enabled, the claims are not enabled. Noticeably absent in the Office Action, however, is any citation of case law supporting this interpretation of the enablement requirement of 35 U.S.C. §112, first paragraph. Indeed, ***Applicants are only required to enable the claimed inventions***. In applying the enablement requirement, ***the "invention" that must be enabled is that defined by the claims***. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987). The Examiner is reminded that claim 25 is directed to methods of "enhancing penetration of an antisense nucleic acid across the alimentary canal of an animal" and that claims 66 and 82 are directed to methods of "delivering an antisense nucleic acid to the intestinal mucosa."

Applicants' specification amply enables the claimed methods. The Declaration of Dr. Hardee and Dr. Teng showed that the claimed pharmaceutical compositions, in fact, enhance penetration of a nucleic acid across the alimentary canal of an animal. Paragraphs 3-5 of the Declaration describe experiments whereby penetration of an oligonucleotide across the alimentary canal of rats and dogs is enhanced by delivery of the oligonucleotide along with at least two fatty acids. Such examples are also set forth in Applicants' specification in Examples 3, 4 and 13. Indeed, the Office Action acknowledges that the specification "does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway" (see, page 3 of the Office Action). Thus, Applicants have amply enabled the claimed inventions. Further, one skilled in the art is not required to perform, and Applicants are not required to enable, gene therapy to practice the claimed inventions. Thus, no amount of undue experimentation is required to practice Applicants' claimed inventions. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

DOCKET NO.: ISIS-3105 **PATENT**

IV. Conclusion

It is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 40, 56, and 78 have been cancelled.

Claim 82 has been added.

Claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80 have been amended as follows:

25. (Amended four times) A method of enhancing penetration of [a] an antisense nucleic acid across the alimentary canal of an animal comprising administering to said animal the composition of claim 44, wherein said composition enhances penetration of said nucleic acid across the alimentary canal of said animal.

50. (Amended) The composition of claim 49 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

54. (Amended) The composition of claim 44 wherein said composition is [proylene] propylene glycol based.

61. (Amended twice) A composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has [at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification] a modified nucleobase or a modified sugar residue.

63. (Amended) The composition of claim 62 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

64. (Amended) The composition of claim 61 wherein said nucleic acid has [at least one chemical modification selected from the group consisting of a modified nucleobase, a modified sugar residue, and a modified backbone linkage] a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

66. (Amended) A method of delivering [a] an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said [oligonucleotide] nucleic acid has at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification.

74. (Amended) The method of claim 73 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

76. (Amended) The method of claim 66 wherein said composition is [proylene] propylene glycol based.

80. (Amended) The method of claim 66 wherein said composition further comprises a bile salt.

82. (New claim) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.